Remarks

Claims 1, 3-7, 20, 21, 24-27, 57-59, and 61-65 are pending. **Please note that claim 59 is pending, contrary to the list of pending claims in the Office Action.** Claims 1, 26 and 62 have been amended. Claim 21 has been withdrawn from consideration as being drawn to a non-elected invention.

Claims 1 and 62 have been amended to refer to a bi-domain peptide which contains a first domain that binds to heparin and heparin-like compounds with high affinity and a second domain that binds to the substrate. Support for this amendment can be found in the specification at least at page 17, lines 11-18 and page 3, lines 10-14. Claims 1 and 62 have been further amended to specify that the protein growth factor or the peptide fragment thereof binds with low affinity to the heparin or heparin-like polymer. Support for this amendment can be found in the specification at least at page 4, lines 10-12.

Claim 26 has been amended to refer to the heparin-like polymers in the plural form and to delete "derivative thereof".

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 1, 3-7, 20, 21, 24-27, 57-59, and 61-65 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

One of ordinary skill in the art knows the types of compounds that are considered derivatives of dextran sulfate, chondroitin sulfate, heparin sulfate, fucan, and alginate. However,

claim 26 has been amended to delete the term "derivative thereof" and to refer to the heparin-like polymers in plural form. The plural form for the listed heparin-like polymers (i.e. dextran sulfates, chondroitin sulfates, heparin sulfates, fucans and alginates) encompasses natural and synthetic forms of the polymers and their derivatives. Therefore, claim 26 as amended is definite.

Claims 1 and 62 have been amended to recite that the domain on the growth factor with low affinity for heparin binds to the heparin or heparin-like polymer, as suggested by the Examiner. Therefore, claims 1 and 62 as amended are definite.

Rejection Under 35 U.S.C. § 103

Claims 1, 3-7, 20, 24-27, 57, 58, and 61-65 were rejected under 35 U.S.C. § 103(a) as being obvious over Schroeder-Tefft et al., *J. Controlled Release* 48:29-33 (1997) ("Schroeder-Tefft") in view of Kwon et al., *J. Controlled Release* 22: 83-94 (1992) ("Kwon") and DeBlois et al., *Biomaterials* 15:9 (665-672) (1992) ("DeBlois"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The claimed compositions and methods

The claims are directed to drug delivery compositions and methods. The compositions contain a substrate, a bi-domain peptide with a domain the binds with heparin or heparin-like compounds with high affinity and a domain that covalently binds to the substrate, heparin or a heparin-like compound, and a growth factor that binds with heparin with low affinity. Binding

to heparin with "low affinity" is defined in the claims to mean that at a NaCl concentration of 25 mM to 140 mM the peptide does not bind to heparin.

Schroeder-Tefft

Schroeder-Tefft discloses complexing heparin to TGF-β2 and then mixing this complex with a matrix material, such as collagen, to stabilize the TGF-β2 so that it remains biologically active longer than it does when it is free. Collagen serves as a tissue scaffold (see page 297, col. 1, para. 1). Schroeder-Tefft does not teach including a bi-domain peptide that contains a heparin-binding domain and domain which covalently binds to the substrate.

Kwon

Kwon teaches ionically binding positively charged polypeptides and proteins to negatively charged microspheres formed of albumin or albumin and heparin (see page 84, col. 1, para. 3-4). The albumin and heparin form a microsphere. Kwon does not teach the inclusion of a bi-domain peptide that covalently binds with albumin. Additionally, Kwon does not teach the inclusion of a protein growth factor or fragment thereof which binds to heparin with a low affinity.

DeBlois

DeBlois is directed at the delivery of fibroblast growth factor (FGF), a heparin-binding growth factor (see page 665, col. 2). DeBlois discloses (a) mixing heparin and FGF and then mixing this solution into fibrinogen before clotting (p. 666, col. 1, para. 3) and (b) collagen sponges to which fibrin is attached, followed by the addition of FGF and/or heparin (see page

666, col. 2, para. 3). DeBlois does not teach or suggest the inclusion of a bi-domain peptide that binds covalently to the matrix and that binds heparin or a heparin-like compound with high affinity. Nor does DeBlois teach or suggest the inclusion of a protein growth factor which binds to heparin with a low affinity.

The Combined References

The combination of Schroeder-Tefft with Kwon and DeBlois does not teach nor suggest the claimed compositions and methods. None of the references teach a bi-domain peptide with a heparin-binding domain and a domain that covalently binds to the substrate. Kwon and DeBlois do not disclose protein growth factors that bind to heparin with a low affinity. Thus, the combination of the references does not teach or suggest a composition that contains (a) a substrate, (b) a bi-domain peptide that is covalently bound to the substrate, where the peptide contains a heparin-binding domain and a domain that covalently binds to the substrate, (c) heparin or a heparin-like polymer, and (d) a protein growth factor or portion thereof that binds to heparin or the heparin-like polymer with a low affinity for heparin. Therefore the claims as amended are non-obvious over Schroeder-Tefft in view of Kwon and DeBlois.

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AMENDMENT AND RESPONSE TO OFFICE ACTION

Allowance of claims 1, 3-7, 20, 21, 24-27, 57-59, and 61-65, as amended, is respectfully solicited.

Respectfully submitted,

Rivka D. Monheit
Reg. No. 48,731

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HOLLAND & KNIGHT LLP
One Atlantic Center, Suite 2000
1201 West Peachtree Street
Atlanta, Georgia 30309-3400
(404) 817-8514
(404) 817-8588 (Fax)

Certificate of Facsimile Transmission

I hereby certify that this Amendment and Response to Office Action, and any documents referred to as attached therein are being facsimile transmitted on this date, September 8, 2003, to the Commissioner for Patents, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450.

Pam Turnbough

Date: September 8, 2003

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